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Oral vitamin D - Is it necessary to be taken with meals containing fat?

Gnädinger, M ; Bossert, F ; Eichmann, F ; Haug, B ; Krüsi, M ; Nadig, M ; Pazeller, S ; Ringli, T ;
Ruppli, M ; Salzgeber, M ; Schmid, I ; Schöb, R ; Wälti, B ; Zeller, M

Abstract: Vitamin D is fat-soluble. It is suggested to be taken with meals containing fat to enhance its intestinal absorption. However, there are only a few controlled studies which investigate prandial inferences on its absorption. Within a group of 13 general practitioners, during a period of three months, we ran two identical study protocols during winter and early springtime. Blood was taken from the subjects, 60'000 units of vitamin D (cholecalciferol) in 3 ml of oil was ingested, and blood was sampled once again a week later. In a randomized cross-over design, one time the vitamin was ingested postprandially, and another time in a fasting state. The basal levels of 25-hydroxyvitamin D were 45 (28) (median, interquartile range) before fasting, and 40 (15) nmol/l before postprandial dosing. One week thereafter, serum 25-hydroxyvitamin D was increased by 13 (21), when the supplement was ingested in a fasting state, while taken after a meal containing fat, the rise was 25 (17) nmol/l (n.s., $p=0.13$). The other parameters which were tested remained unchanged throughout the study: calcium, phosphate, albumin, and 1,25-dihydroxyvitamin D (calcitriol). Our preliminary data do not support major influences on vitamin D absorption by the influence of fasting vs. concomitant fatty meal intake. Vitamin D oral loading doses can be applied irrespective of prandial state, while its maintenance dosing by the patients should still take place after a meal containing fat. Absorption of vitamin D seems to be unpredictable – fractionate dosage and determination of 25-hydroxyvitamin D during treatment may be helpful. Unexplained low serum levels after repeated supplementation could be due to intestinal disease, mainly celiac.

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Corresponding Author:

Dr. Markus P Gnadinger,
Study Director, Institute for General Medicine University of Zurich, Pestalozzistr. 24, Zurich, 8091 - Switzerland

Submitting Author:

Dr. Markus P Gnaedinger,
Free Coworker, Institute for General Medicine University of Zurich, Pestalozzistr. 24, Zurich, 8091 - Switzerland

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None.

Oral vitamin D - Is it Necessary to be taken with Meals Containing Fat?

Author(s): Gnadinger MP, Bossert F, Eichmann F, Haug B, Krüsi M, Nadig M, Pazeller S, Ringli T, Ruppli M, Salzgeber M, Schmid I, Schöb R, Wälti B, Zeller M

Summary

Vitamin D is fat-soluble. It is suggested to be taken with meals containing fat to enhance its intestinal absorption. However, there are only a few controlled studies which investigate prandial inferences on its absorption.

Within a group of 13 general practitioners, during a period of three months, we ran two identical study protocols during winter and early springtime. Blood was taken from the subjects, 60'000 units of vitamin D (cholecalciferol) in 3 ml of oil was ingested, and blood was sampled once again a week later. In a randomized cross-over design, one time the vitamin was ingested postprandially, and another time in a fasting state.

The basal levels of 25-hydroxyvitamin D were 45 (28) (median, interquartile range) before fasting, and 40 (15) nmol/l before postprandial dosing. One week thereafter, serum 25-hydroxyvitamin D was increased by 13 (21), when the supplement was ingested in a fasting state, while taken after a meal containing fat, the rise was 25 (17) nmol/l (n.s., $p=0.13$). The other parameters which were tested remained unchanged throughout the study: calcium, phosphate, albumin, and 1,25-dihydroxyvitamin D (calcitriol).

Our preliminary data do not support major influences on vitamin D absorption by the influence of fasting vs. concomitant fatty meal intake. Vitamin D oral loading doses can be applied irrespective of prandial state, while its maintenance dosing by the patients should still take place after a meal containing fat. Absorption of vitamin D seems to be unpredictable – fractionate dosage and determination of 25-hydroxyvitamin D during treatment may be helpful. Unexplained low serum levels after repeated supplementation could be due to intestinal disease, mainly celiac.

Introduction

There are no natural food sources which guarantee an optimal supply of vitamin D to the populations of most

industrialized countries. We depend on sunlight for vitamin D production via UV-B radiation. But in regions of latitudes higher than 45°, sunlight does not enable people to produce sufficient amounts of vitamin D from autumn through spring. Thus, because the half-life of vitamin D is about one month, nearly all inhabitants of these regions will get vitamin D levels in the insufficiency (<50 nmol/l) or deficiency (<25 nmol/l) ranges from winter until spring unless they take supplements [1]. Concerns about skin cancer have caused the widespread use of sun blocks which limit vitamin D synthesis even in the summertime.

Classically, vitamin D deficiency evolves with osteomalacia and osteoporosis or osteopenia, respectively. There are several diseases which are associated with vitamin D deficiency: hypertension, atherosclerosis, diabetes, asthma, colon cancer, multiple sclerosis, migraines, Parkinson's disease, seasonal depression, neurodermitis, psoriasis, collagenosis and susceptibility to infection (especially tuberculosis) [2]. Groups of patients prone to getting hypovitaminosis D include those with sun allergies or skin cancer, transplantation patients (immunosuppressed) who avoid sunlight, dark-skinned or adipose persons, smokers, patients with inflammatory or celiac bowel disease, elderly persons, and especially people who have been institutionalized [3].

Vitamin D is a member of the group of fat-soluble vitamins. This may be a reason for the widespread advice to take it together with a meal containing fat. However we found little published evidence supporting this notion. Stoll et al have recently investigated the nutritional dependency of vitamin D, but the test conditions were not standardized, and the results were only published as a congress poster [4]. Tangpricha et al. found no evidence of food dependency on vitamin D₂ (ergocalciferol) absorption [5]. In contrast, Viegas Ramondo et al described better absorption of Vitamin D₃ (cholecalciferol) when taken with a meal containing 26 g of fat as compared to a meal with only two g of fat [6].

Vitamin D can be administered orally or by intramuscular injection. However, the latter can lead to

painful granuloma at the injection site [7], hemorrhage and infections, and absorption of the vitamin can be delayed. This may explain why injections can result in prolonged therapeutic blood levels of vitamin D as compared to when administered orally [8, 9]. For practical reasons it would be useful if oral vitamin D supplements could be administered independently of meals, e.g. in the practice of the physician who is in care of the patient.

Vitamin D is stored within fat tissue. Its half-life of about one to two months and its lack of toxicity allows it to be given on a daily, weekly or monthly basis. Intestinal absorption of vitamin D seems to follow two phases: firstly, it is rapidly absorbed into the mucosa cells, and later on, it is enclosed into chylomicron particles which are delivered into the thoracic duct. The latter depends on the presence of food triglycerides and therefore also pancreatic and bile enzyme activity within the intestinal lumen [10]. Monounsaturated and saturated fatty acids increase vitamin D absorption as compared to polyunsaturated ones [11]. In contrast to its precursor, 25-hydroxyvitamin D (calcidiol) is transported via the portal vein to the liver, independently from chylomicron particles [10,12,13]. This may explain why it is absorbed more constantly and generally better than its non-hydroxylated precursor molecule [14]. The pharmaceutical industry has produced Fosavance®, a compound containing vitamin D and alendronate, an oral bisphosphonate that must strictly be taken while fasting. Nonetheless, with Fosavance a reproducible and dose-dependent uptake of vitamin D has been demonstrated [15].

Aims of the study: To test in a pilot study whether oral cholecalciferol is absorbed differently when taken in a fasting as compared to a postprandial state.

Subjects and Methods

13 practicing healthy male family physicians (GP), members of the "Quality Circle Oberthurgau" took part in this trial.

Venous blood was drawn and thereafter 3 ml of vitamin D Wild Company (medium cat triglyceride oily drops), containing 60'000 E cholecalciferol, were taken in a fasting or postprandial state. One week later, blood was sampled again. After an interval of three months, the same procedure took place, but the circumstances of supplementation were changed, from fasting to postprandial, and vice versa. In a

randomized order, seven participants started with the postprandial intake.

The following data were registered: age, smoking habits, height, weight, blood pressure, and heart rate. Serum was tested for: calcium, phosphate, albumin, 25-hydroxy- and 1,25-dihydroxyvitamins D.

Null hypothesis

1. The increase in serum 25-hydroxyvitamin D one week after a dose of 60'000 E cholecalciferol in 3 ml of oily solution is not enhanced by a concomitant principal meal containing a variable quantity of fat.
2. The serum levels of 25-hydroxyvitamin D are comparable three months after postprandial vs. fasting dosage of cholecalciferol.

Inclusion criteria: practicing GP, healthy, informed consent.

Exclusion criteria: chronic inflammatory or celiac bowel disease, intake of supplements containing vitamin D, tropical holidays, and solarium visits.

Laboratory methods: serum calcium, phosphate and albumin were assessed with standard laboratory tests. Vitamin D values were determined with AMP RIA CT (1,25 D₃, radioimmunoassay) or ADVIA CENTAUR vitamin D total (25 OH D₃, immunoassay). The latter has an inter-assay variation coefficient (CV) of 5 to 11 % depending on the concentration of 25-hydroxyvitamin D (higher CV with lower concentrations). This was the reason we calculated mean values from duplicate determinations on separate day assays. In the case of discrepancies of more than 15%, a third analysis was done, and the mean value was calculated between the third value and the one closer to it.

Statistics

Values are given as median (interquartile range [IQR]). Differences of the eighth day vitamin D level increases after postprandial vs. fasting vitamin dosage were assessed by paired T-testing, while differences of the three months of vitamin D level increases were analyzed by a simple T-Test. Because this was a pilot study with a closed group of physicians, we did not apply a pre-study power calculation.

Results

13 healthy male GPs participated in the study. The first set of study determinations took place from 1st December 2011 to 1st February 2012, and the dates of the second set were from 24th February 2012 to 17th April 2012. On the second term, one participant erroneously took 200'000 instead of 60'000 units of vitamin D, so the values of his last blood sample were excluded from the study. His individual values (blood levels before and after postprandial vitamin dosing) were: calcium 2.39 / 2.33 mmol/l, 25-hydroxyvitamin D 42 / 131 nmol/l and 1,25-dihydroxyvitamin D 39 / 67 ng/l. In one blood sample, only a single determination of 25-hydroxyvitamin D was possible because of a lack of the quantity of serum; all other determinations took place per protocol.

The baseline data of the participants are summarized in Table 1. One participant is a smoker. When correcting total calcium for albumin values, levels were 2.27 (0.18) or 2.30 (0.14) mmol/l before fasting and postprandial dosing, respectively /l. Values of calcium (either corrected by albumin values or not), phosphate, albumin and 1,25-dihydroxyvitamin D were unchanged throughout the study. The individual courses of 25-hydroxyvitamin D level increases are depicted in Figure 1. Fasting intake of vitamin D resulted in a median increase of 13 (21) nmol/l, while increase after a meal containing fat was 25 (17) nmol/l (n.s., p=0.13). Three months after intake of the first vitamin dose, the increase of 25-hydroxyvitamin D was 9 (19) nmol/l after fasting vitamin intake (n=6) as compared to 7 (21) (n=7) after postprandial intake (n.s.). The time interval between the first vitamin dose and the third blood sampling was 84 (3) days. The time interval after the vitamin ingestion and up until blood sampling was 164 (7) hours for postprandial and 168 (22) for fasting intake (n.s.). 10'000 units of vitamin D given orally were calculated to rising blood levels of 25-hydroxyvitamin D by 2.9 (2.6) nmol/l.

Discussion

Our study has revealed two major insights on vitamin D oral absorption. Firstly, there is no clinically relevant group difference between cholecalciferol postprandial vs. fasting absorption. A loading dose can be applied orally as needed at the doctor's surgery independent of whether the patient has eaten or not. Secondly, there is a large unpredictability of the rise of 25-hydroxyvitamin D levels after single oral supplements.

In their dosage study, Viegas Raimundo et al. did not find any rise in 25-hydroxyvitamin D levels after administering 50'000 E cholecalciferol together with a meal containing 2.6 g fat on day seven or fourteen [6]. In our study, supplements consisted of 60'000 E cholecalciferol in a medium cat triglyceride oily solution, making the quantity of fat similar for both studies. However, in the fasting state, the supplements were administered without a meal. Perhaps the higher fiber content of the low fat meal [6] effectively blocked the absorption of vitamin D as compared to our subjects, who remained in a fasting state for at least another four hours.

A study on prandial inference on vitamin D absorption was conducted by Wagner et al [16]. In elderly patients, 28'000 E cholecalciferol in 1 ml of alcoholic solution was given together with a meal containing fat or in a fasting state for two months on a weekly basis. There was only a minimal difference to support postprandial as compared to fasting ingestion of the supplements.

Denker et al. described a maximal 24-fold individual variation between the areas under the curve of vitamin D serum levels after fasting intake of single cholecalciferol supplements [15], but there was no control group taking vitamin supplements postprandially, because the pills also contained the bisphosphonate alendron, which has to be taken strictly in a fasting state.

For these reasons, it seems wise to fractionate loading doses into several smaller proportions to achieve more reliably target levels of vitamin D. Patients taking oral vitamin D supplements for diseases like osteoporosis or myopathy with a magnesium deficiency must be tested for reaching 25-hydroxyvitamin D target levels, and thereafter the dosages of the supplements should be appropriately adapted. Perhaps in the future, 25-hydroxyvitamin D supplements (calcidiol) will provide more predictable results [14, 17].

In our study, we did not find any difference of 1,25-dihydroxyvitamin D levels before vs. eight day after ingestion of the supplement. Serum levels of this active metabolite of vitamin D however are highly regulated, so in healthy physicians and after a moderate dosage of cholecalciferol, this finding is not surprising.

Limitations

We aimed to conduct our study not under sophisticated experimental conditions, but rather everyday practical ones. So we sent our samples to a commercial laboratory which works together with most of us. Furthermore, the dosage of vitamin D was quite low (60'000 E are close to the twofold recommended monthly dose). These circumstances and the large variability of the laboratory determinations of 25-hydroxyvitamin D [18, 19] impaired to some degree our being able to make clear conclusions from our analysis. Within the lower range of serum levels as measured in this study, the manufacturer's brochure mentions a CV of 11.1%. This value compares to the 36 % (fasting) to 59 % (postprandial) increases in 25-hydroxyvitamin D serum levels one week after dosing. As a security measure, we did double or (when necessary) triple determinations of 25-hydroxyvitamin D.

Post-hoc power analysis revealed that with the given variability of vitamin D absorption and only 12 participants, we had only a 40% chance of detecting prandial differences of 33% and more, and the study was therefore underpowered.

We used Wild oily vitamin D drops in our study for two main reasons: Firstly, we wanted to use preparations which were accessible to general practitioners. Secondly, we had no ethical committee permission for this study (this would have implied getting a Swissmedic drug authority notification), which led us to use only preparations admitted for the given indication (i.e. oral supplementation in suspected vitamin D deficiency), the given dosing and the given route of administration. ViDe3® alcoholic drops are also admitted for oral supplementation, but 60'000 E of them would contain ca. 10 ml of alcohol which per se could affect gastrointestinal absorption of vitamin D and would be unacceptable for the participants.

In some institutions in Switzerland, it is a common practice to start vitamin D therapies by orally administering a loading dose of injectable vitamin D ampoules (Streuli) containing 300'000 E cholecalciferol dissolved in 1 ml of medium chain triglycerides. 0.2 ml would contain the same amount of vitamin D as used in our protocol, but measuring and applying it by the participants would have entailed severe accuracy problems. Furthermore, the ampoules are only admitted for parenteral use.

Our experimental solution contained 3 ml of oil. Indeed, intake of a similar quantity of lipids (0.3 ml/min of duodenal Intralipid® 10%, corresponding to 0.25

kcal/min or 0.03 g/min of soybean oil) caused a slight but not persistent rise in cholecystokinin serum concentrations and perhaps gall bladder contraction [20]. This could have blurred the effect of prandiality in our study data. But if this was the case, the question whether vitamin D could also be administered orally to fasting subjects would have to be answered in the affirmative, provided that a similar quantity of oil is given concomitantly with the vitamin.

Or subjects were instructed to administer the postprandial vitamin dosing after a principal meal containing fat, however the composition of the meal was not specified to them.

We did not measure blood levels of vitamin D (cholecalciferol), so we were not able to distinguish its absorption differences from those in 25-hydroxylation metabolism. Perhaps the interval of eight days was too short to produce stable 25-hydroxyvitamin D serum levels, since 14 days after dosage 25-hydroxyvitamin D levels were still rising, as demonstrated by Viegas Raimundo et al [6]. However, since our subjects were their own controls, and three months after ingestion of the first vitamin D supplement there was no significant difference in the serum levels achieved, this seems not to be a source of major concern for our data.

Conclusions

Our preliminary data do not support major influences on vitamin D absorption by the influence of fasting vs. concomitant fatty meal intake. Vitamin D oral loading doses can be applied irrespective of prandial state, while its maintenance dosing by the patients should still take place after a meal containing fat. However, individual absorption of vitamin D seems to be unpredictable – fractionate dosage and determination of 25-hydroxyvitamin D serum levels during treatment may be helpful. Hence, as vitamin D is cheap and non-toxic; small differences in its intestinal absorption may not be clinically relevant. Unexplained low 25-hydroxyvitamin D levels after repeated supplementation could be due to intestinal disease, mainly celiac.

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List of abbreviations

1. GP: general practitioner
2. CV: coefficient of variation
3. IQR: Interquartile range

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Illustrations

Illustration 1

Figure 1. Individual increases of serum 25-hydroxyvitamin D after 8 days as compared to pre-dosage levels (n=12).

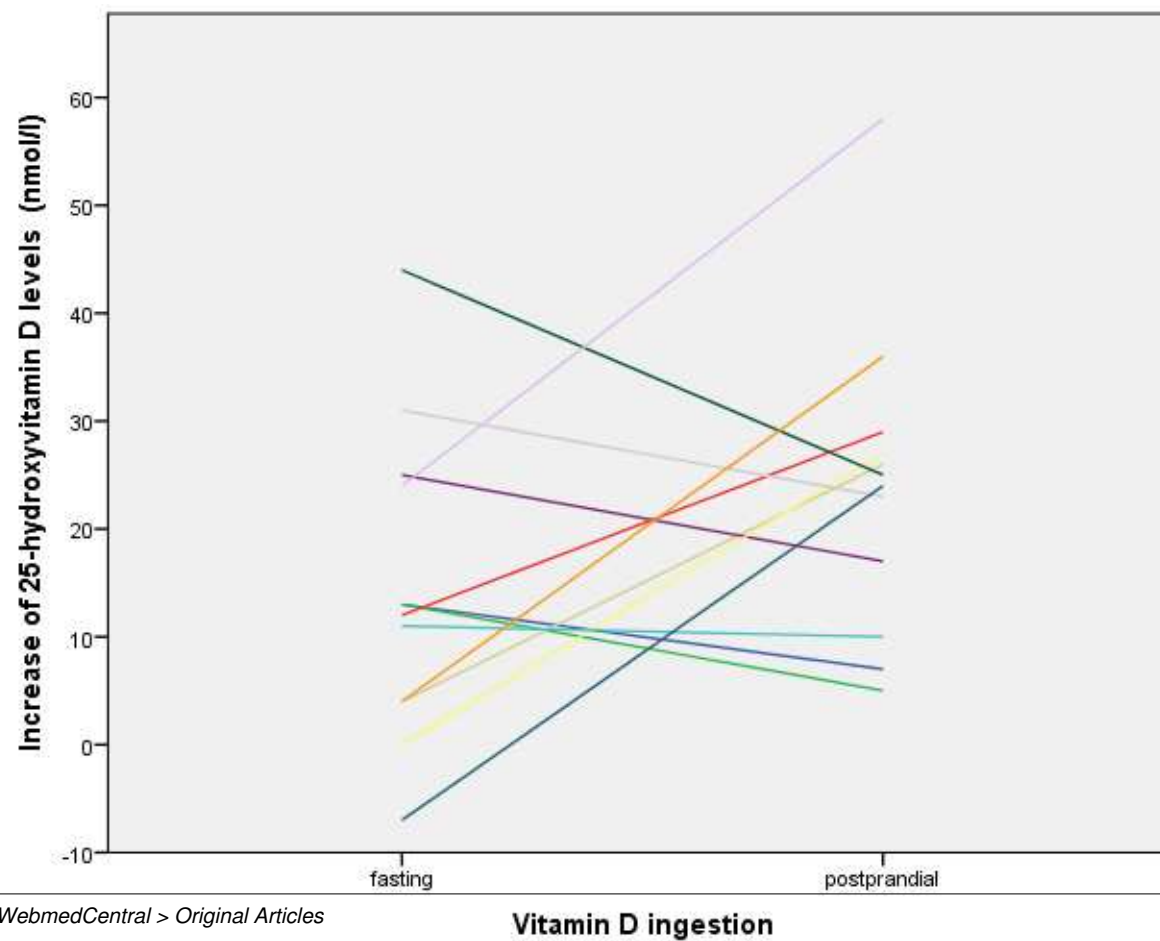


Illustration 2

Table 1. Baseline values (n=13)

Age, years	55 (7)	
Body mass index, kg/m ²	23.1 (3.3)	
Blood pressure, mmHg	130 / 84 (21 / 12)	
Heart rate, min ⁻¹	72 (20)	
<i>Study phase</i>	<i>before fasting dosing</i>	<i>before postprandial dosing</i>
Serum calcium, mmol/l	2.37 (0.12)	2.40 (0.12)
Serum phosphate, mmol/l	1.15 (0.20)	1.15 (0.37)
Serum albumin, g/l	43.5 (3.0)	44.5 (4.3)
25-hydroxyvitamin D, nmol/l	45 (28)	40 (15)
1,25-dihydroxyvitamin D, ng/l	38 (26)	39 (16)

Median values (IQR), n=12.

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